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AMBULATORY PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE.

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THEOPHYLLINE SERUM CONCENTRATIONS IN AMBULATORY
PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE

by

James Wolfe Bredon

A Thesis Submitted to the Faculty of the
DEPARTMENT OF PHARMACY PRACTICE
In Partial Fulfillment of the Requirements
For the Degree of
MASTER OF SCIENCE
WITH A MAJOR IN PHARMACY
In the Graduate College
THE UNIVERSITY OF ARIZONA

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STATEMENT BY AUTHOR

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Finally, and most importantly, it is with much love and heartfelt gratitude that I dedicate this work to my wife, Edean, to my children, Margaret and Michael, who were born during its course, and to my father and the memory of my mother. Without their presence, in body and in spirit, it would never have been completed.

*Quid dulcius hominum generi a natura datum est quam
sui cuique liberi?*

- Cicero

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ABSTRACT

A two-part study was designed to investigate the application of theophylline serum concentration data at a Veterans Administration Medical Center. The investigation was unique in using ambulatory patients as study subjects in assessing the use of these laboratory tests.

As has been found in other studies which examined different drugs and involved hospitalized subjects, this investigation discovered significant problems in the ordering, application, and documentation of these data when judged against established criteria. Of significance also are the findings which suggest a positive correlation between the proper use of these tests and improvement in patient outcome, and the demonstrated relationships between clinical symptoms and sub-therapeutic and toxic serum concentrations of theophylline.

CHAPTER 1

INTRODUCTION

Theophylline is a naturally occurring alkaloid which has been used medicinally in the past to produce a variety of pharmacologic responses. These include stimulation of the central nervous system, action on the kidney to promote diuresis, stimulation of the cardiac muscle, and smooth muscle relaxation (Goodman and Gilman, 1980). More effective and safer agents have largely replaced theophylline in its stimulant and diuretic actions, but it is still advocated and widely used for its ability to relax smooth muscle in the bronchial tree, resulting in bronchodilation (Hinshaw and Murray, 1980).

Theophylline, aminophylline (water-soluble theophylline ethylenediamine) and several more recently developed methylxanthine derivatives are used principally in contemporary therapeutics to treat the acute and chronic effects of bronchial asthma and any reversible bronchoconstrictive component of diseases causing obstruction of the pulmonary airways (Ingram, 1980).

A review by Ogilvie (1978) reported on a variety of studies which have demonstrated the beneficial effects of theophylline and its analogs. However, a major concern

among prescribers of these drugs has been the toxicity associated with their use in some patients (Sheiner, 1980). Adverse reactions ranging in severity from mild to fatal have been reported (Merrill, 1943; Yarnell and Chu, 1975; Jacobs, Senior and Kessler, 1976; Iberti and Hammond, 1978). Furthermore, a report by Zwillich et al. (1975) demonstrated that serious toxicity in the form of generalized seizures can occur without being preceded by signs of less severe reactions. The 50% mortality rate and seizures resistant to anticonvulsant therapy made this form of theophylline toxicity of particular concern to these authors.

Therapeutic effectiveness and toxicity have been shown to correlate closely with the concentration of theophylline in serum (Jenne et al., 1972; Jackson et al., 1964; Levy and Koysooko, 1975). Bronchodilation is thought to be minimal at 5 mcg/ml (Mitenko and Ogilvie, 1973a), whereas concentrations in the "therapeutic range" of 10 to 20 mcg/ml are considered to be most effective (Sheiner and Tozer, 1978). Above 20 mcg/ml adverse reactions become a threat and are more prevalent and severe as concentrations increase past this point (Kordash, Van Dellen and McCall, 1977; Weinberger et al., 1976).

Achievement of serum concentrations within the relative narrow range necessary for safe and effective therapy with these drugs is made more difficult by the

large variations in serum concentrations found among individuals equivalently dosed. Age, cardiovascular and pulmonary status, level of tobacco use, presence of liver disease or obesity, type of diet and concurrent use of certain drugs are all thought to effect theophylline disposition (Powell, et al., 1978; Kappas et al., 1976; Weinberger et al., 1977; Cummins, Kozak and Gilman, 1977; Landay, Gonzales and Taylor, 1978; Nielsen-Kudsk, Magnussen and Jacobsen, 1978; Gal, Jusko and Yurchak, 1978).

These factors point to the necessity for individualizing dosage regimens with these drugs, and the availability of laboratory assays for theophylline in serum which are accurate, reasonable in cost and rapidly done, have made the use of these assays an important tool in efforts to provide optimum therapy (Hendeles, Weinberger and Johnson, 1978; Koch-Weser, 1975). Trained clinical observation combined with the proper use of theophylline serum concentration data has been shown to be effective in providing relief of broncho-constriction while avoiding toxicity (Wyatt, Weinberger and Hendeles, 1978).

Studies concerned with the application of serum concentrations to make dosage recommendations have raised questions about the appropriate use of this technology. Examination of the sampling process and use of the data obtained from assays for gentamicin, digoxin and phenytoin

in four separate studies (Wilson and Wilkinson, 1974; Anderson, Hodges and Barnes, 1976; Flynn et al., 1978; Slaughter, Schneider and Visconti, 1978). demonstrated significant problems in terms of the correct utilization of serum drug concentrations for making rational therapeutic decisions. Omitted information on the laboratory order, inappropriate times for obtaining samples, or the lack of a rational indication for performing the assay resulted in data being unusable for many patients. The absence of indications that assay results were ever used to effect therapy or acknowledged in any way was also demonstrated as a frequent problem. Each of these studies, however, was done using hospitalized patients as study subjects.

Purpose

There are no available reports assessing the application of serum concentration data in ambulatory patients. Theophylline and its congeners are frequently used in outpatients to treat chronic obstructive pulmonary diseases over extended periods of time. This investigation was conducted to achieve the following objectives:

Phase I

1. To assess the appropriateness of the use of theophylline serum concentration data in a series of ambulatory patients under treatment for chronic

obstructive pulmonary disease at a Veterans Administration Medical Center.

2. To compare Pulmonary physicians with General Medicine physicians in terms of their use of theophylline serum concentration data.

Phase II

1. To assess the ability of physicians practicing at the study hospital to determine which patients are at risk from sub-therapeutic or toxic serum concentrations, as shown by the decision to request a laboratory determination.
2. To determine if the signs and symptoms noted by physicians in their physical assessments of the study subjects could be related to the theophylline serum concentrations found in these patients.

CHAPTER 2

RELATED LITERATURE

Background

Theophylline was demonstrated to relax bronchial smooth muscle by independent researchers in the United States and Germany (Macht and Ting, 1921; Hirsh, 1922). It was not until the results of two clinical trials were published (Herrmann, Aynesworth and Martin, 1937; Greene, Paul and Faller, 1937) that the drug began to gain acceptance and subsequently became a popular treatment for bronchospasm.

Theophylline has a variety of other pharmacologic effects and these have been exploited clinically in the past (Ziment, 1978), but the drug is still most widely used in contemporary therapeutics as a bronchodilator. The bronchodilator effect of theophylline was shown to be related to its concentration in human serum in a study reported by Turner-Warwick (1957). Progressive improvement in pulmonary function has been shown to occur in hospitalized asthmatics as serum theophylline concentrations increase from 5 to 20 mcg/ml, although the patients in this study were asymptomatic at the time of the study (Mitenko and Ogilvie, 1973a). Weinberger and Bronsky (1974) reported

a study of asthmatic children in which peak serum theophylline concentrations averaging 13 mcg/ml were effective in reducing asthmatic symptoms, whereas peak concentrations averaging 6.5 mcg/ml were relatively ineffective.

Serum concentrations between 8 and 20 mcg/ml have been shown to relieve bronchoconstriction in adult subjects (Jenne et al., 1972; Bulow, Larsson, and Leideman, 1975). Pollock, Kiechel and Cooper (1977) reported a study in which theophylline serum concentrations in excess of 10 mcg/ml inhibited exercise-induced bronchospasm. Jenne's work also revealed that variations in serum theophylline concentrations of 2.9 to 32.6 mcg/ml could result from maintenance doses ranging from 200 to 300 mg every 6 hours (Jenne et al., 1972) indicating the necessity for individualizing therapy with this drug.

In a recent study (Scherr, Scherr, and Morton, 1980) dosing of oral theophylline to achieve serum concentrations in the 10 to 20 mcg/ml range was assessed as a "major factor allowing reduction or discontinuance of corticosteroid therapy in asthmatic children." Ekwo and Weinberger (1978) reported theophylline to be the only medication required by 70% of 172 pediatric asthmatics to control chronic symptoms. In addition to bronchodilation, theophylline as an aminophylline infusion has been observed to improve the ventilatory response of the lungs of normal subjects to hypoxia

and hypercapnea (Lakshminarayan, Sahn and Weil, 1978). Theophylline treatment has also been reported to provide substantial relief from the dyspnea associated with pulmonary emphysema (Sapoznik, 1960; Keenan, 1962). More recent studies attempting to assess theophylline therapy in this disease have been more conservative in the investigators' evaluation of the results. A study of 10 patients with demonstrated "irreversible" airway obstruction showed a 6% mean maximal increase in forced expiratory volume at one second (FEV_1) with low (9.0 to 12.5 mcg/ml) peak serum theophylline concentrations (Eaton et al., 1980). High peak concentrations (17 to 22 mcg/ml) resulted in a 21.3% mean increase. Even though pulmonary function tests showed improvement, the patients were not able to subjectively distinguish between placebo and theophylline treatment. In light of the lack of evidence for alteration in the course of the disease from treatment (Emirgil et al., 1969), the authors questioned the rationale of theophylline treatment where no subjective improvement occurs in the symptoms of emphysema.

Alexander, Dull, and Kasik (1980) also advised against institution of maintenance theophylline therapy for "irreversible airway obstruction" before carefully monitored therapeutic trials have been conducted. They observed

that 6 of 40 patients responded to oral theophylline treatment, as revealed by improvement in FEV_1 . These investigators also found no subjective improvement in their patients with peak serum theophylline concentrations averaging 15.1 ± 4.2 mcg/ml.

Schmidt and Altschuler (1980) observed pulmonary function and clinical response in 12 patients with irreversible chronic obstructive pulmonary disease randomized between oral theophylline and placebo. The double-blind crossover study showed 7 of 11 patients completing the trials to have improved clinically on active drug, while one subject reported improvement on placebo. Analysis by the investigators indicated no statistically significant differences between placebo and active drug in either pulmonary function tests or clinical evaluation, but the authors state the results to be "suggestive" of deterioration in pulmonary function while subjects were taking placebo, and increased exercise tolerance and decreased dyspnea while on theophylline.

Toxicity

Enthusiasm for the effectiveness of theophylline has been tempered by the drug's potential for toxicity. Merrill (1943) reported the sudden deaths of three patients after intravenous administration of aminophylline.

Seizure activity prior to death was not reported by Merrill, but three other cases of sudden death from intravenous aminophylline were reported by Bresnick, Woodard and Sageman (1948) in which premonitory convulsions did occur. These authors also noted that the speed with which the drug had been administered may have been a factor.

White and Daeschner (1956) described twenty cases of pediatric poisoning by aminophylline in which four of the children died. The poisonings had resulted from either oral, rectal, intramuscular or intravenous administration and three of the four deaths were due to oral or rectal use. The authors suggested dosing the drug less frequently "to prevent an accumulative effect." In reporting another death from rectal administration of aminophylline in a child, McKee and Haggerty (1957) suggested that "a method available for determining blood levels of theophylline may be useful in cases of suspected aminophylline poisoning."

Thus, theophylline has been identified with serious toxicity since the earliest history of its use as a therapeutic agent. More recent studies have also been concerned with theophylline toxicity. An investigation of the predisposing causes of cardiac arrest in 132 critically ill patients disclosed that 12 of 20 drug-induced cardiac arrests were due to aminophylline administration (Camarata et al., 1971). The authors reported that "slow

administration" (over 3 to 5 minutes) of "established doses" (250 to 750 mg) were responsible and suggested that the route of administration and speed of infusion may have accounted for this high incidence of severe toxicity.

Jenne et al. (1972) observed in a group of 83 subjects that only those with trough serum concentrations greater than 13 mcg/ml while on oral aminophylline therapy exhibited signs of drug-related toxicity, and that adverse reactions were "very common" in patients with concentrations greater than 20 mcg/ml. The authors state that determination of theophylline serum concentrations is a worthwhile procedure in patients with severely disabling bronchospasm.

A case of severe theophylline toxicity manifested by repeated grand mal seizure activity was reported in a patient receiving the "ordinary recommended dosage" (Jacobs and Senior, 1974). The patient, a 72 year old man, was taking oral theophylline 240 mg every 6 hours. At the time of repeated seizure activity the patient's serum theophylline concentration was 86 mcg/ml. Even though laboratory analyses showed normal liver function, the authors concluded he had impaired hepatic metabolism of theophylline and suggested that measurement of serum concentrations of the drug would have permitted recognition before the complication.

Schwartz and Scott (1974) described 4 patients in whom intravenous aminophylline administration was thought to be the cause of status epilepticus. Although serum concentration data were not obtained, cessation of aminophylline therapy resulted in eventual complete recovery from seizure activity in three patients. The fourth patient died due to continuous convulsions and respiratory failure after administration of 2 grams of aminophylline intravenously over a 10 hour period. The authors emphasized that aminophylline should always be suspected as a cause of seizures in adult asthmatics, as well as in children.

The results of serum theophylline determinations in 8 patients who developed grand mal seizures while on intravenous aminophylline therapy showed a range of 25 to 70 mcg/ml, with a mean value of 53 mcg/ml (Zwillich et al., 1975). In comparing these patients with a group of 15 others in whom serum theophylline concentrations were also determined, it was found that 4 patients with less severe drug-related reactions (nausea, severe headache) had serum concentrations from 31 to 38 mcg/ml while concentrations in the 11 patients without adverse effects ranged from 13 to 31 mcg/ml, with a mean of 19 mcg/ml. The authors suggested that the frequent occurrence of congestive heart failure and liver dysfunction in the

seizure group may have predisposed these patients to unusually high serum concentrations. This study showed the correlation of the theophylline serum concentrations with toxicity in this group of patients. Further, the authors emphasized that in only one of the eight patients who suffered seizures were there any prodromal signs of toxicity, pointing out the danger of recommending "mild toxicity" as an end point for theophylline therapy (Franklin, 1974). Since seizures were not controlled with anticonvulsants and were fatal in 4 of the 8 patients, this was deemed an unsafe practice and it was suggested that monitoring serum theophylline concentrations was valuable in individualizing therapy.

Yarnell and Chu (1975) reported that generalized focal motor seizures in 6 patients were related to intravenous or rectal administration of aminophylline. All patients were described as "essentially neurologically stable" at the onset of seizures. Three patients had serum theophylline concentrations of 21.5, 31.5 and 61 mcg/ml on the day seizures began. Seizures were resistant to "large doses of intravenous anticonvulsants", and 5 of the 6 patients died. One survivor was transferred to a nursing home with a "neurological residual." Concluding their report, the authors stated that "it can be difficult to obtain the the desired therapeutic bronchodilator response and avoid

possible toxicity because of individual variation in metabolism and unpredictability of blood levels with a repeated dose regimen. Therefore, careful individual monitoring of aminophylline dose and administration rate is essential."

Jacobs, Senior, and Kessler (1976) undertook a study which attempted to relate theophylline dosage to serum concentration and toxicity. Fourteen of the 47 hospitalized adults retrospectively evaluated were deemed to have had adverse reactions to theophylline (or aminophylline). The authors noted that similar doses resulted in wide variations in serum concentrations. In all patients with toxic reactions the serum concentrations exceeded 15 mcg/ml, but concentrations were greater than 25 mcg/ml in 11 of the 14 patients who exhibited toxicity. The authors suggested the data from this work shows that "proper dosage is best guided by knowledge of plasma concentration".

Efforts to alleviate the problem of toxicity to theophylline and its congeners have been complicated by dosage recommendations which are too high for many patients (Hendelees and Weinberger, 1980). Mitenko and Ogilvie (1973a) concluded from their research that an intravenous loading dose of 5.6 mg/kg followed by a maintenance dose of 0.9 mg/kg per hour would result in serum theophylline concentrations of 10 ± 5 mcg/ml in 95% of adult patients. These doses were endorsed in a major medical journal (Azarnoff,

1973) and subsequently widely used. The recommendations from this study were based on data from nine young patients who were not acutely ill at the time of the investigation. A subsequent study (Hendele et al., 1977) showed unacceptably high serum concentrations resulted when these doses were used in older, acutely ill, hospitalized chronic obstructive pulmonary disease patients. Concentrations above 20 mcg/ml occurred in 14 of the 48 patients, and the authors also emphasized the poor correlation between dose and serum concentration of theophylline, as well as a strong relationship between these concentrations and toxicity.

Factors Influencing Theophylline Serum Concentration

The large variations in serum concentrations seen in subjects given similar doses of theophylline or aminophylline has led to efforts to discover what factors peculiar to individual subjects may be responsible for altering the pharmacokinetics of this drug. Theophylline has been determined to be eliminated primarily by metabolism in the liver, with about 10% lost as unchanged drug in the urine (Brodie, Axelrod and Reichenthal, 1952; Jenne Nagasana and Thompson, 1976). As would be expected, diseases or other influences in hepatic function have been shown to alter the theophylline disposition. Mangione, et al. (1978) found the theophylline elimination half-life

to be prolonged in cirrhotic patients. Normal subjects showed a half-life averaging 6.0 hours, whereas cirrhotic patients had a half-life of theophylline which averaged 28.8 hours. The body clearance for the drug was also low in cirrhotics, showing a mean of 18.8 ml/kg/hr, as compared to a mean of 63.0 ml/kg/hr in normal subjects.

Smoking habits, either of tobacco or marijuana, have been demonstrated to increase the rate of metabolism of theophylline by as much as 50 to 70 percent, depending upon the rate of consumption of these substances (Hunt, Jusko and Yurchak, 1976; Powell et al., 1977; Jusko et al., 1978). Patients over 50 years of age were shown to be spared from this effect in one report (Pfeifer and Greenblatt, 1978) as were obese individuals in a separate study (Gal, Jusko, Yurchak and Franklin, 1978). Since tobacco smoke contains polycyclic hydrocarbons which are known to induce the hepatic microsomal enzyme system, it is thought that the effect of smoking to increase theophylline clearance is mediated through the liver.

A diet high in charcoal broiled meats also increased elimination (Kappas et al., 1978) and it was suggested that the hydrocarbon content of these foods may be responsible for hepatic enzyme induction. A further study of the dietary influence on theophylline metabolism found no appreciable difference when fats were substituted for carbohydrates in the controlled solid food diets of 6

subjects (Anderson, Conney and Kappas, 1979). A high carbohydrate diet was also found to have no effect, but when a high protein diet (50% of total caloric intake) was given the subjects, the elimination half-life of theophylline was decreased by 1.4 to 2.5 hours. Since no changes were found in the apparent volumes of distribution of theophylline, the authors suggest these differences resulted from acceleration of hepatic drug metabolism. An earlier study had also shown a high protein diet to significantly speed theophylline elimination (Kappas et al., 1976). This work also indicated a high carbohydrate-low protein diet slowed the elimination rate.

Welling et al. (1975), in an attempt to assess the influence of diet and fluid intake on the bioavailability of theophylline found that a "standard high protein diet" containing 53% protein resulted in more rapid and complete absorption of the drug than a high carbohydrate or high fat diet.

Since phenobarbital is known to induce hepatic enzymes and this drug is contained in several oral bronchodilator combinations, studies have examined the possibility of an effect on theophylline degradation. Greene et al. (1977) found no change in theophylline clearance when phenobarbital was added to subjects' theophylline therapy. However, Landay, Gonzales and Taylor (1978) found a mean

increase of 34% in clearance in 6 subjects after phenobarbital treatment. Piafsky, Sitar and Ogilvie (1977) found no significant effect of oral phenobarbital administration on the disposition of intravenous aminophylline doses, but qualified their results with the suggestion that a study should be made of the effect of phenobarbital in patients receiving oral theophylline on a long-term basis.

Other drugs have been reported to alter theophylline pharmacokinetics. Studies with erythromycin revealed a reduced rate of elimination of theophylline from plasma (Cummins, Kozak and Gillman 1976; Kozak, Cummins and Gillman 1977) when these drugs were given concomitantly. Weinberger et al. (1977) also reported this to occur with troleandomycin. When 3 commonly used antibiotics (tetracycline, erythromycin and cephalixin) were studied to determine if they effected theophylline disposition, no statistically significant evidence of an effect was found (Pfeifer, Greenblatt and Friedman, 1979). Since data from some subjects showed a reduced clearance of theophylline with tetracycline and erythromycin, the investigators advised that "clinically important interactions do occur in some susceptible individuals."

A recent case report (Sugar et al., 1980) involving elevated theophylline serum concentrations and persistent severe nausea in a man aged 71 was thought to be due to

concurrent administration of thiabendazole. Since there had been no other changes in treatment or the patient's status, nor was thiabendazole found to interfere with the theophylline assay in use, thiabendazole-induced inhibition of theophylline metabolism in the liver was suspected.

The possibility that allopurinol might interfere with theophylline metabolism has been questioned (Marlin, Hartnett and Berend, 1978). Two studies (Grygiel et al., 1979; Vozeh et al., 1980) which investigated this possibility found no evidence that allopurinol effected theophylline disposition. The Grygiel study did find that the amount of the theophylline metabolite 1-methylxanthine was increased, and it was proposed that allopurinol inhibited a xanthine oxidase mediated step in a secondary stage of theophylline metabolism.

Obesity has also been suggested to effect theophylline disposition. Work done by Gal et al. (1978) indicated that total body clearance appeared unchanged but that apparent volume of distribution and mean half-lives were increased in obese subjects. They advised that many obese patients may require less frequent dosing to maintain a therapeutic serum concentration, based on their findings. They also concluded that since the volume of distribution of theophylline corresponded to total body weight rather than to ideal body weight, the drug distributes into body fat. Conversely, Jusko et al. (1979) concluded from results

of their study using younger obese subjects with no additional impairments to health, that clearance of theophylline may actually increase in such individuals. According to these investigators, this is consistent with the findings that obese individuals have increased cardiac output and a resulting increase in hepatic blood flow (Alexander et al., 1962). They also comment that the opposite finding in the previous study may have been due to the presence of "confounding factors" in the subjects used, although the nature of these factors was not specified.

In studying 9 patients with severe pulmonary edema following acute left ventricular heart failure, Piafsky et al. (1977a) observed that plasma half-lives following treatment with intravenous aminophylline infusions were longer than those of 19 normal subjects. Decreased plasma clearances were also found, but peak serum concentrations and apparent volumes of distribution were not different in the two groups. The authors suggested alterations in theophylline disposition in acute pulmonary edema may be due to hepatic congestion or decreased delivery of drug to the liver, and that repeated doses or constant infusions of aminophylline should not be used in patients so affected.

A suggestion was made by Hendeles et al. (1977) that one of the predisposing factors to increased

theophylline serum concentrations and resultant toxicity was severe, uncompensated congestive heart failure, although the results did not conclusively demonstrate this effect. More concrete evidence was reported in a study which looked at the effects of congestive heart failure and other factors on theophylline disposition (Powell et al., 1978). The mean theophylline clearance value for 3 patients diagnosed with severe congestive heart failure was 26.5 ± 13.5 ml/kg per hour. After successful treatment, the mean clearance for these patients was 66.4 ± 24.7 ml/kg per hour. These investigators also reported that a diagnosis of severe airways obstruction or pneumonia was correlated with significant decreases in clearance of theophylline and that cigarette smoking caused an increase in clearance in their subjects. Jusko et al. (1979) also found congestive heart failure to be a "major factor accounting for decreased theophylline clearance in older adults" and suggested that hepatic congestion and diminished hepatic blood flow may account for this reduction.

As was observed by Powell et al. (1978) certain pulmonary diseases may alter theophylline disposition, although their research found that less debilitating conditions such as asthma and bronchitis had no effect. Two earlier works (Weinberger et al., 1976; Hendeles et al., 1977) also suggested that a diagnosis of chronic obstructive

pulmonary disease predisposed patients to toxic plasma concentrations from theophylline doses which have been shown to be safe in healthy subjects.

The effect of age on theophylline disposition has been examined. Premature infants had very low clearance values (Aranda et al., 1976), whereas children aged 1 to 9 years diagnosed as asthmatics had clearances which were higher than those of adults. Older children had clearances similar to adult subjects (Zaske et al., 1977). Jusko (1977) advised lowering doses for patients over 50 years of age, but two other studies were interpreted by the investigators to show no justification for altering doses in older patients (Piafsky et al., 1977a; Powell et al., 1978).

The possibility that a patient's sex may effect theophylline disposition has also been investigated. Hendeles et al. (1977) reported slower rates of elimination in critically ill females and recommended reduced dosages. Two studies by Powell et al. (1977; 1978) found no significant differences between males and females in theophylline clearance, or apparent volume of distribution.

Since dietary methylxanthines share metabolic pathways with those of theophylline administered medicinally, the effect of ingestion of a diet free of those compounds was studied (Monks, Caldwell and Smith, 1979). This investigation found an increase in the rate of elimination

of theophylline when foods containing caffeine, theobromine and theophylline were removed from subjects' diets. This indicates, according to the authors, that competition for the same enzyme systems between dietary and therapeutic methylxanthines produces an effect on theophylline elimination which may be important clinically.

The suggestion that theophylline metabolism may be subject to a potentially saturable enzymatic pathway has led to a review of studies which showed evidence of this effect (Lesko, 1979). The evidence compiled in this review led the author to conclude that "dose-dependent" elimination kinetics may occur with theophylline and that clinicians should be aware of this possibility when dosage adjustments are made. Unexpectedly large changes in plasma concentration may occur following dose adjustments, especially after long-term use of theophylline.

In addition to the factors discussed which have an effect on theophylline disposition, studies have been reported which indicate significant variation in theophylline clearance within the same subjects, even in the absence of these factors. When studied over time (1 to 8 months) Leung, Kalisker and Bell (1977) found significant intra-individual changes in theophylline clearance rate in 12 children with asthma. Loren et al. (1977) also studied pediatric asthmatics and found serum theophylline

concentrations to vary by more than 6 mcg/ml in 11 of 24 children over a period of 1 to 8 weeks. They recommended close monitoring of serum concentrations in such patients to effectively control asthmatic symptoms and avoid toxicity.

Application of Serum Concentration Data

A variety of approaches have been used to assess the utility of serum drug concentration data. Bootman et al. (1979) addressed the questions raised for the need for this information in clinical practice. Specifically, these authors analyzed possible benefits from individualizing gentamicin therapy using serum concentrations. The investigators concluded that knowledge of this data, when used to adjust dosage, not only decreased the incidence of adverse reactions to gentamicin but improved the outcome of therapy.

Smith (1975) examined information generated by the Boston Collaborative Drug Surveillance Program concerning toxicity to digitalis glycosides. The Massachusetts General Hospital joined this program in October 1970 and 250 digoxin treated patients were monitored as of June 1972. Adverse reactions to digoxin were reported in 15 (5.9%) of these patients. In the two year period 1966 to 1968, there were 64 of 459 monitored patients (13.9%) who had adverse reactions to digoxin (Koch-Weser, Sidel and Sweet, 1969). The significant decrease in the latter period was

thought to be due to the use of serum digoxin concentrations, a capability unavailable at the hospital in the earlier study (Koch-Weser, Duhme and Greenblatt, 1974).

Lund, Jorgensen and Kuhl (1964) used serum concentration data and patient counseling to assess therapy with phenytoin in epileptics. Counseled patients had therapeutic concentrations significantly more often than patients who were not counseled, and the authors attributed the differences to use of concentration data and improved compliance.

A compliance study has also been done using theophylline concentrations (Sublett et al., 1979). Fifty children coming to a pediatric emergency room complaining of wheezing were randomly selected, and 37 were determined to have been prescribed appropriate doses of theophylline. Five of 37 had serum concentrations in the 5 to 10 mcg/ml range and none were in the 10 to 20 mcg/ml range. This was judged to be the result of poor compliance to the prescribed regimen.

Two reports (Floyd and Cohen, 1977; Koup et al., 1976) have been published in which the authors describe the systematic use of theophylline serum concentration data to design individual dosage schedules. This approach was successful in their subjects by providing effective therapy without toxicity, and they advocated the routine use of

these assays as a part of a systematized effort to guide therapy.

In attempting to assess the impact of a pharmacokinetics service upon the use of serum theophylline assays, Bearce et al. (1979) found assays to be more appropriately used in an institution with a pharmacokinetics service as compared to a similar hospital which did not have this service. The investigators judged that costs could be reduced by using this service to prevent unnecessary or erroneous orders, and that care could be improved by maintaining more patients within the therapeutic range of theophylline serum concentrations.

Sheiner et al. (1979) proposed and tested a method to predict serum concentrations using previously acquired data on drug concentrations, in addition to the traditional methods of predicting individual variation in pharmacokinetics from sex, age, and renal disease. The complex mathematical method is intended for automated application but the point made was that when previous drug concentration data is combined with other variables in the prediction of future concentrations, there is a significant improvement in the outcome of this attempt. Using digoxin as an example, the authors found that the use of one measured concentration, as opposed to none, improved forecasting accuracy for future concentrations by 40%, and data from two previous

concentrations improved the precision by 67%. The use of only one previous concentration was found to be more important in forecasting future concentrations than any observable patient feature, such as sex, age or renal function.

Many studies have demonstrated the utility of drug serum concentration determinations, but few have been dedicated to the assessment of inappropriate application. Wilson and Wilkinson (1974) designed a study to evaluate the effectiveness of an institution's drug delivery system by measuring compliance with prescribed drug regimens. Ninety-two patients (18 adults and 74 children) with seizure disorders and associated mental or neurological deficits were studied. The system was found inadequate in its ability to provide these patients with optimal therapy of primidone, phenobarbital and/or phenytoin as assessed by either clinical parameters or serum drug concentrations. More importantly, the availability of drug concentrations to the medical staff resulted in practically no improvement. In fact, 12% of patients with low concentrations had a further decrease in dosage, and 25% of those with appropriate concentrations also had a decrease in dosage. The majority of patients with high concentrations of phenytoin or phenobarbital had no dosage adjustment. A change in dosage was made in 22% of situations showing appropriate serum

concentrations. When an adjustment was made subsequent to the availability of this information, it was made in the wrong direction for 45% of the patients on phenytoin and for 20% of those on phenobarbital. They conclude that "it is apparent that information about serum concentrations had little effect on the number or direction of dose changes for diphenylhydantoin and phenobarbital in these epileptic subjects."

Anderson, Hodges, and Barnes (1976) reported their findings evaluating the use of gentamicin concentrations drawn from 62 patients. Of 212 samples drawn for serum gentamicin concentration determination, the authors judged that in 23 (10.8%) of the samples indications were lacking for performing the assay. Of the 212 samples drawn, 110 (51.9%) were judged to be incorrectly drawn for proper interpretation. Eighty-five (40.1%) of the results were ignored (not acknowledged in the patient's record and no change in therapy) and 26 (41.9%) of the 62 samples correctly drawn and not ignored were acted upon appropriately. As interpreted by these investigators, their findings show that 42 (19.8%) of the 212 samples were used to make appropriate decisions regarding therapy of these patients.

Remarkably similar results were reported by Flynn et al. (1978) who studied 44 patients given 52 treatment courses of gentamicin. Although the capability existed

for performance of gentamicin serum concentrations in the institution evaluated, it was surprising that in 38 (73%) of the 52 courses of treatment, no assays were ordered. Of the 45 concentrations determined during the study, five (11%) were single samples and were judged to be inadequate for monitoring therapy. Seven (31%) of 20 samples which were appropriately drawn had results reported back to the physician too late to have any impact on therapy, 49% of the determinations were considered usable, and 22% of the 45 concentrations done were judged to have been acted upon appropriately.

Finally, in a study by Slaughter, Schneider, and Visconti (1978) 145 digoxin or digitoxin serum concentration assays were examined. Of these, 125 samples (86%) were drawn under steady-state conditions, and further evaluation was performed for 120 of the appropriately drawn sample assays. In 89 assays which should not have resulted in a change in dose, 87 (98%) were correctly interpreted. The dose was decreased in two cases. Thirty-one assays should have resulted in a change in dose, but the dose was unchanged in 11 (36%). In addition, the authors judged that 49% of the assays had been originally ordered for irrational or inappropriate reasons. They concluded that there is substantial evidence of misuse of digoxin assays in clinical practice.

To summarize, theophylline has been shown to be an effective drug, but one with potential for serious toxicity. Demonstration of a narrow therapeutic range and the strong correlation of serum concentration with effect on bronchodilation and toxicity makes use of assays for theophylline in serum an important patient management tool. The knowledge that a variety of exogenous and endogenous factors can effect theophylline disposition makes judicious application of theophylline serum concentration determinations even more essential. As has been demonstrated in studies on a few of the other drugs for which these assays are frequently used, there is justification for concern about the appropriateness of use of this data in hospitalized patients. There is little information reported which addresses the use of these assays in ambulatory patients.

CHAPTER 3

DESIGN OF STUDY

Introduction

This study was conducted in a 325-bed general medical-surgical Veterans Administration Medical Center. The subjects were ambulatory patients under care from the hospital's outpatient clinics. In the first phase of the study outpatient medical records were retrospectively reviewed to collect data describing the ordering process, documentation, and interpretation of theophylline serum concentration determinations. Physicians practicing in the Pulmonary Clinic site were compared to those practicing in the General Medicine Clinics in terms of their application of this technology.

In the second phase data were collected to enable comparison of theophylline serum concentrations in two groups of patients. One group had theophylline assays ordered by the physician, while the second did not have this test ordered by the physician. The assays were then obtained by the investigator in this second group. In making this comparison, the ability of physicians to accurately determine which patients are at risk from

sub-therapeutic or toxic theophylline serum concentrations using known medical history and symptoms was assessed. Further, an attempt was made to examine the relationship between the signs and symptoms noted in the physician's physical assessment of the patient and the serum concentration of theophylline found in that patient.

Methodology--Phase I

The first phase of this investigation involved review of the medical records of 100 patients. For this purpose patient numbers (corresponding to Social Security numbers) were obtained from the clinical laboratory files of patients who had a theophylline serum concentration assay performed in the period from September 1, 1979 to April 30, 1980. Only those assays reported as being ordered for outpatients were included. The medical records for these patients were requested and reviewed initially for diagnosis. Only those patients with a diagnosis of chronic obstructive pulmonary disease and for whom an oral formulation of theophylline, aminophylline or oxtriphylline had been prescribed were selected for inclusion in the first phase of the study. The records of the first 100 patients who met these criteria were then further reviewed and the following information recorded: age, sex, height, weight, diagnosis of other chronic or acute illnesses, other medications used,

smoking history, theophylline product prescribed and directions for use, and the date and result of the laboratory report of the theophylline serum concentration assay in the patient's file. To assess the utilization of these assays, the following information was also obtained from review of these records:

1. Was a reason given for requesting the theophylline assay?
2. If a reason was stated, what was it?
3. Was the time the blood was drawn for the assay recorded?
4. Was the time the patient took his last dose prior to having blood drawn recorded?
5. Were results of the assay acknowledged and interpreted by the physician in the progress notes?
6. Was a change made in the patient's dosage when a change was indicated by the result of the assay?

(For this purpose a theophylline serum concentration in the 10 to 20 mcg/ml range was considered therapeutic, and a concentration in the 5 to 9.9 mcg/ml range was considered therapeutic if the patient had been assessed by the physician as having responded.)

7. If a change in the dose was made, was it increased or decreased in the appropriate direction, as indicated by the assay?

8. Was the patient assessed by the physician as being improved, unchanged or deteriorating on his or her next appointment for pulmonary examination?

The data were gathered, tabulated and the information reported as a descriptive assessment of the appropriateness of use of these assays. To determine how appropriately General Medicine physicians used theophylline assays as compared to Pulmonary physicians, their responses to criteria 1 through 7 were subjected to chi-square analysis. The null hypothesis of no differences between these two groups of physicians in response to these criteria was tested. Inability to reject the null hypothesis would suggest that Pulmonary physicians do not use theophylline assays more or less appropriately than General Medicine physicians.

Methodology--Phase II

Phase II of the study began July 1, 1980 and continued through October 1980. Patients who presented to the outpatient pharmacy at the hospital a prescription for an oral theophylline, aminophylline or oxtriphylline product were interviewed by the investigator. Patients who had not been taking one of these drugs for at least the preceding two weeks were not considered for inclusion in the study. Patients who had been seen in the outpatient clinics and reported having a blood sample drawn for a theophylline

serum concentration became part of the pool of subjects from which the "Physicians' Group" was selected. This group of subjects was determined from clinical laboratory records which revealed all patients who had had a theophylline serum concentration assay performed as an outpatient. Those patients who had been seen in the outpatient clinic regarding their pulmonary condition and who had not had blood drawn for a theophylline assay on their most recent appointment were asked to participate in the study. The study was explained, and if the patient reported taking the theophylline product regularly since his or her previous appointment, they were asked to read and sign an Informed Consent Form allowing their participation (Appendix A). If the patient agreed, a 10 ml blood sample was obtained from the patient and the laboratory request was completed showing the theophylline product used, dosage, time of last dose, time the sample was obtained, date, patient name and identification number. These patients comprised the "Investigator's Group" in this study. Samples were taken to the clinical laboratory where they were centrifuged and the sera separated. Theophylline serum concentrations in the samples were determined in duplicate using the Syva Emit enzyme immunoassay for theophylline. This method utilized the Aminco Rotochem IIa Parallel Fast Analyzer and Syva's Emit Theophylline Assay Reagent, Catalog No. 6p019. This

assay determines the amount of theophylline present in serum by measuring the activity of glucose-6-phosphate dehydrogenase isolated from a bacterial source. A sample of serum is added to a reagent (Reagent A) containing substrate and an excess of antibody directed against the drug. The unreacted antibody is then added to a solution (Reagent B) containing glucose-6-phosphate dehydrogenase to which theophylline has been attached in a position where interaction with the antibody inactivates the attached enzyme. The residual enzymatic activity is proportional to the original serum concentration of theophylline. If the duplicate assays agreed within 10 percent, the result was reported as an average of the two results. If agreement was not within 10 percent, the assay was repeated. The accuracy of this assay, as performed by the Clinical Laboratory personnel, was examined for 309 observations from July to October 1980. At a theophylline serum concentration of 20.0 mcg/ml, the coefficient of variation was 4.50%. Further examination of 35 samples over a five-day period yielded the results shown in the following table. One lot of reagent was used to test reconstituted control sera at the three levels indicated in Table 1.

The medical records of patients for whom theophylline serum concentrations were ordered by the investigator (Investigator's Group) and those of the patients

Table 1. Results of 35 Samples over a Five-day Period.

	Level I	Level II	Level III
Mean Concentration	7.05	14.20	26.01
Standard Deviation	±0.20	±0.35	±0.75
Coefficient of Variation	2.84%	2.46%	2.88%
[C.V. (%) = $\frac{\text{Std. Dev.}}{\text{Mean Conc.}} \times 100$]			

who had assays ordered by their physician (Physicians' Group) were reviewed for the following information: age, sex, height, weight, diagnosis of active chronic or acute illnesses, other medications used, smoking history, and the physician's assessment of the patient's pulmonary status at the most recent examination. Changes were recorded (as noted by the physician) which revealed improvement or deterioration in the patient in symptoms of dyspnea or shortness of breath, coughing, sputum production, wheezing or exercise tolerance. The following was also noted for patients having theophylline assays ordered by the physician: reason the assay was ordered, theophylline product prescribed and directions for use, time of sampling and time of last dose for the assay, and results of the assay.

The chi-square procedure and Student's "t test" were used to test the null hypothesis of no differences between the investigator's and physicians' groups in terms of the numbers of patients from each group who had sub-therapeutic (below 10 mcg/ml), therapeutic (10 to 20 mcg/ml) and toxic (above 20 mcg/ml) theophylline serum concentrations. Inability to reject the null hypothesis would support the conclusion that physicians at the study hospital may not be able to accurately determine which ambulatory patients are at risk from low or high theophylline doses from information available to them at examination.

Chi-square analysis was also used to determine if physicians' assessments of either increasing shortness of breath or symptoms of theophylline toxicity could be associated with non-therapeutic theophylline serum concentrations. The null hypothesis of no differences in the numbers of patients who had non-therapeutic theophylline serum concentrations who either had or did not have these symptoms was tested. Inability to reject the null hypothesis would suggest that the presence of any of these signs was not necessarily associated with theophylline serum concentrations outside of the therapeutic range.

Limitations

1. Only patients with a diagnosis of "chronic obstructive pulmonary disease", "chronic bronchitis", or "emphysema" noted on the active problem list in the medical record were included in the study, and all patients were under treatment from outpatient clinics of the Tucson Veterans' Administration Medical Center.

2. Only one theophylline assay was considered in the study for any individual patient. If a patient had more than one assay performed during the study period only the most recent assay value was considered in analysis.
3. It was assumed for purposes of comparison that the physician staffing remained static during Phase I and Phase II of the study, although the staff may have changed in the interim between Phase I and Phase II.
4. Much of the data analyzed in this study was collected retrospectively, and the limitations of this technique should be considered when results are interpreted.
5. Although the theophylline assay used in the study was determined to be accurate for clinical purposes, there is some error involved in its use. This must also be considered in interpretation.
6. It was assumed in Phase II that time intervals after doses were equally dispersed between the investigator's and physicians' groups.

Definitions

A bronchodilator is any drug which has the property of increasing the diameter of the lumen of the pulmonary air passages.

Clearance is the removal of a substance (drug) from blood or plasma by metabolism or excretion, expressed as volume per unit time.

Chronic bronchitis is a condition associated with excessive tracheobronchial mucus production sufficient to cause cough with expectoration for at least 3 months of the year for more than 2 consecutive years.

Chronic obstructive pulmonary disease is a condition in which there is chronic obstruction to airflow due to chronic bronchitis and/or emphysema.

Dyspnea is a difficult or labored breathing, used in describing these symptoms in a clinical setting.

Elimination half-life is the time necessary to reduce a drug's concentration in the blood or plasma by 50 percent.

Emphysema is a disease resulting in an anatomic alteration of the lungs characterized by abnormal enlargement of the air spaces distal to the terminal respiratory bronchioles, often accompanied by destructive changes of the alveolar walls.

Plasma is the fluid portion of blood, as distinguished from suspended material.

Serum is plasma from which fibrinogen has been separated during clotting.

CHAPTER 4

RESULTS AND DISCUSSION

This study was designed to be conducted in two parts, referred to as Phase I and Phase II. The results from each phase of the investigation will be reported and discussed, in the order the study was undertaken.

Phase I

In the first phase of this study the medical records of 100 ambulatory patients under treatment for chronic obstructive pulmonary disease were reviewed to assess the use of theophylline serum concentration data at a Veterans Administration Medical Center. All 100 medical records reviewed were those of patients who, at the time of data collection, were under medical care from either the Pulmonary or General Medicine Outpatient clinics. Fifty patients were from the Pulmonary clinics and 50 patients were from the General Medicine clinics. The study criteria dictated that patients have a diagnosis of chronic obstructive pulmonary disease on the active problem list. Further, a current prescription for an oral methylxanthine derivative must have been in effect for the patient. All patients were male with ages ranging from 46 to 82 years, with a mean ($\pm$ S.D.) age of 62.5 ± 8.2 years. Pulmonary patients' ages ranged from

47 to 82 years, with a mean ($\pm$ S.D.) age of 62.3 ± 8.8 years. General Medicine patients' ages ranged from 46 to 79 years, with a mean ($\pm$ S.D.) age of 62.8 ± 7.5 years.

Appendix B, Table B-1, shows the active diseases or problems diagnosed in the study patients and the frequency of their occurrence. Appendix B, Table B-2 shows the oral methylxanthine drugs available at the study hospital during the period of the investigation, and the frequency with which they were prescribed in the study patients.

Review of medical records against the study criteria established to evaluate the use of theophylline assay data produced the following results. Sections 1 through 8 correspond numerically to the individual criterion or factor examined (Chapter 3: Methodology).

1. In 65% of the 100 medical records reviewed, there were no statements indicating the reason the theophylline assay had been ordered. Table 2 shows the breakdown, by physician specialty, of response for this criterion. Chi-square analysis revealed no significant difference between Pulmonary and General Medicine physicians in this criterion ($\chi^2 = 0.176$; $df=1$; n.s.).
2. Thirty-five charts (35%) had documentation of the reason the theophylline serum concentration assay

Table 2. Response, by Physician Specialty, to Criterion 1
(Statement of Reason for Assay Order)

Physician Specialty	Reason Stated	No Reason Stated	Total
Pulmonary	19 (38.0%)	31 (62.0%)	50 (100.0%)
General Medicine	16 (32.0%)	34 (68.0%)	50 (100.0%)
Total	35 (35.0%)	65 (65.0%)	100 (100.0%)

$\chi^2=0.176$; df=1; n.s.

was requested. Table 3 shows what these reasons were and the number of times each was given by each physician group. None of the stated reasons were judged to be irrational or inappropriate for requesting the determination of a theophylline serum concentration. There were 9 (25.7%) of these assays which had no time reported for the patient's last dose, making interpretation impossible. Six of these were requested by the General Medicine Clinic and 3 by the Pulmonary Clinic.

3. All of the 100 laboratory reports reviewed recorded the time the blood was drawn for the assay. When patients reported to the outpatient phlebotomist, the time was stamped on each laboratory report by a time clock just prior to the actual drawing of the blood sample.
4. Twenty-six laboratory reports (26%) had no indication of the time the patient had taken his last dose of theophylline prior to the time blood was taken for the assay. Table 4 shows how physicians responded, by specialty, to this criterion. When subjected to chi-square analysis, no statistically significant difference was found between the two physician categories in response to this criterion.

Table 3. Reasons Given for Assay Orders and Frequency

Reason Stated	Frequency		
	Pulmonary	General Medicine	Total
Evaluation of therapy	7 (20.0%)	4 (11.4%)	11 (31.4%)
Increasing dyspnea	3 (8.6%)	5 (14.3%)	8 (22.9%)
Exacerbation of COPD	6 (17.2%)	2 (5.7%)	8 (22.9%)
Suspected toxic reaction	2 (5.7%)	5 (14.3%)	7 (20.0%)
Compliance check	1 (2.8%)	0 (0.0%)	1 (2.8%)
Total	19 (54.3%)	16 (45.7%)	35 (100.0%)

Table 4. Response of Physicians to Criterion 4 (Documentation of Time of Last Dose)

Physician Specialty	Response		Total
	Time Noted	No Time Noted	
Pulmonary	38	12	50
General Medicine	36	14	50
Total	74	26	100

$\chi^2=0.052$; $df=1$; n.s.

5. Sixty-four (64%) of the 100 records had no indication that the theophylline assay was acknowledged or interpreted, up to and including the time of the patient's next appointment after the assay was requested. Table 5 shows the physicians' responses to this criterion. Chi-square analysis again revealed no statistically significant difference between the two physician groups in fulfillment of this criterion.
6. Of 61 patients who had theophylline serum concentrations outside of the 10 to 20 mcg/ml range 13 (21.3 percent) were above 20 mcg/ml, 13 were below 5 mcg/ml and 35 (57.4 percent) were in the range of 5 to 9.9 mcg/ml. Thirty-two (52.5 percent) of the 61 patients outside of the 10 to 20 mcg/ml range had no changes ordered in their theophylline dosage in response to the report. Of these 32 patients, 5 (15.6 percent) had a concentration below 5 mcg/ml, 6 (18.8 percent) were above 20 mcg/ml and 21 (65.6 percent) were in the 5 to 9.9 mcg/ml range. Six patients (18.8 percent) had been assessed by the physician as having adequately responded to theophylline therapy and therefore required no adjustment in dosage. These 6 were all Pulmonary Clinic patients and had

Table 5. Response of Physicians to Criterion 5 (Acknowledge and/or Interpret Assay on Follow-up)

Physician Specialty	Response		Total
	Assay Interpreted	Assay Not Interpreted	
Pulmonary	19 (38.0%)	31 (62.0%)	50 (100.0%)
General Medicine	17 (34.0%)	33 (66.0%)	50 (100.0%)
Total	36 (36.0%)	64 (64.0%)	100 (100.0%)

$\chi^2 = 0.043$; df =1; n.s.

theophylline serum concentrations in the 5 to 9.9 mcg/ml range. Table 6 shows the comparison of assay results as they occurred in patients from the Pulmonary and General Medicine Clinics. Table 7 compares the Pulmonary and General Medicine physicians as they acted upon reports of theophylline serum concentrations outside of the 10 to 20 mcg/ml range, as reflected by a change in dosage. When subjected to chi-square analysis, these data showed no difference between physicians based on specialty ($\chi^2=0.022$; $df=1$; n.s.).

7. Table 8 shows the direction of dosage changes made in response to reported theophylline serum concentrations. There were a total of 41 dosage changes made in the 100 patients observed. Of the dosage changes made, 25 (61%) were judged appropriate (dose increased when concentration less than 10 mcg/ml and decreased when concentration greater than 20 mcg/ml). The remaining 16 dosage changes (39%) were judged inappropriate, since no justification was found in these patients' medical records for the changes made. Chi-square analysis (Table 9) revealed no difference between Pulmonary and General Medicine physicians in making dosage changes judged

Table 6. Study Patients Categorized by Assay Result

Range of Theophylline Serum Concentration (in mcg/ml)	Number of Patients in this Range		
	Pulmonary	General Medicine	Total
Less than 5	4 (30.8%)	9 (59.2%)	13
5 to 9.9	18 (51.4%)	17 (48.6%)	35
10 to 20	21 (53.8%)	18 (46.2%)	39
Greater than 20	7 (53.8%)	6 (46.2%)	13
Total	50	50	100

Table 7. Dosage Changes in Response to Theophylline Serum Concentrations Below 10 mcg/ml and Above 20 mcg/ml

Physician Specialty	Response		
	Dose Changed	Dose Not Changed	Total
Pulmonary	13 (44.8%)	16 (55.2%)	29 (100.0%)
General Medicine	16 (50.0%)	16 (50.5%)	32 (100.0%)
Total	29 (47.5%)	32 (52.5%)	61 (100.0%)

$\chi^2 = 0.022$; df = 1; n.s.

Table 8. Direction of Dosage Changes in Response to Theophylline Serum Concentration

Theophylline Serum Concentration (mcg/ml)	Response		Total
	Dose Increased	Dose Decreased	
Less than 5	7 (87.5%)	1 (12.5%)	8 (100.0%)
5 to 9.9	13 (92.9%)	1 (7.1%)	14 (100.0%)
10 to 20	7 (58.3%)	5 (41.7%)	12 (100.0%)
Greater than 20	2 (28.6%)	5 (71.4%)	7 (100.0%)
Total	29 (70.7%)	12 (29.3%)	41 (100.0%)

Table 9. Comparison of Physician Groups, by Specialty, in Dosage Adjustments Judged Appropriate and Inappropriate

Physician Specialty	Dosage Adjustment		Total
	Appropriate	Inappropriate	
Pulmonary	13 (61.9%)	8 (38.1%)	21 (100.0%)
General Medicine	12 (60.0%)	8 (40.0%)	20 (100.0%)
Total	25 (61.0%)	16 (39.0%)	41 (100.0%)

$\chi^2 = 0.038$; df = 1; n.s.

to be appropriate or inappropriate, according to study criteria ($\chi^2 = 0.038$; $df = 1$; n.s.).

8. To assess the outcome of changes in dosage which were judged "appropriate" or "inappropriate", the physician's assessment of the patient, classified as improved, unchanged, deteriorated or "no assessment", were compared with appropriate and inappropriate designations in the 41 patients who had dosage changes. These results are shown in Table 10. As assessed by physicians, 16 patients (64%) of 25 who had appropriate changes were improved in symptoms of chronic obstructive pulmonary disease or suspected toxicity to theophylline. Three patients (12%) deteriorated with appropriate dosage changes, and 6 patients (24%) were unchanged. Four (25%) of the 16 patients who had inappropriate changes were assessed as improved, while 6 patients (37.5%) had deteriorated. Five patients (31.2%) were said to remain unchanged with an inappropriate dosage adjustment, and one patient had not returned for examination and therefore had no assessment in the medical record. The categories designated as "deteriorated", "unchanged", and "no assessment" were combined to permit chi-square analysis. This

Table 10. Physician's Assessment of Patient's Condition after Appropriate and Inappropriate Changes in Theophylline Dosage

Classification of Dosage Change	Physician's Assessment		
	Improved	Deteriorated, Unchanged or No Assessment	Total
Appropriate	16 (64.0%)	9 (36.0%)	25 (100.0%)
Inappropriate	4 (25.0%)	12 (75.0%)	16 (100.0%)
Total	20 (48.8%)	21 (51.2%)	41 (100.0%)

$\chi^2 = 4.481; df = 1; p < 0.05$

procedure showed a significant difference in the response of patients who had appropriate changes in dosage as compared to those who had inappropriate changes ($\chi^2 = 4.481$; $df = 1$; $p < 0.05$).

The finding that 65 percent of the medical records reviewed had no reason for requesting a theophylline assay suggests that insufficient documentation of this information occurs frequently in treatment of ambulatory patients at the study hospital. Although the physician originating the order for these assays may have a sound basis for doing so, documentation of these data are important for subsequent treatment of the patient. A patient is often examined by a different physician at his next appointment, and appropriate action is more likely to be taken if it is known that a theophylline serum concentration determination was ordered and also what prompted the order.

When the reasons for requesting these assays were documented by the physicians at the study hospital, none of these reasons were judged to be irrational or inappropriate (Table 3). This contrasts with findings from a study by Slaughter, Schneider, and Visconti (1978) in which the authors concluded that 49 percent of the assays requested for digoxin or digitoxin serum concentrations were originally ordered for inappropriate reasons. This suggests that the

physicians in the current study who were conscientious in documentation also exhibited knowledge of the accepted justifications for ordering theophylline assays and the useful information which these assays can provide. Physicians who neglected to document their reasons for ordering the assay may or may not have had this knowledge.

In addition to the results presented, data from the entire group of 100 patient records were examined to determine in what percentage of the assays were all of the established criteria fulfilled. That is, how many had adequate documentation of what prompted the order, what the outcome was and what action was taken, as well as the percentage in which the laboratory request was complete. A total of 28 (28 percent) of the assays were judged to have been properly accomplished in every respect, according to the study criteria. The Pulmonary physicians and General Medicine physicians were evenly divided, each group having 14 assays which fulfilled all the criteria.

The finding that 64 percent of the records reviewed showed no evidence that the assay result had been reviewed or interpreted provides additional support for the conclusion that documentation is frequently not accomplished or that the assays are simply ignored or forgotten after they are ordered. In either case, the outcome could be detrimental to the patient by allowing him to continue at

a sub-therapeutic or toxic theophylline serum concentration. In a study by Anderson, Hodges, and Barnes (1976) in which they attempted to evaluate the application of gentamicin serum concentrations, the authors judged that 85 of 212 samples (40.1%) had never been acknowledged in terms of assay results after the request had been made. It could be argued that in both the Anderson study and the one reported here that the physician could have reviewed the assay result and made the correct decision based on the available information without documenting this fact. However, it is reasonable to expect that an appropriate dose change (therefore an appropriate decision) is more likely to occur if there is written evidence of any assays ordered and subsequent interpretation, even if the concentration is judged to be appropriate for the patient and no changes are made in therapy.

Although each of the laboratory slips in the patients' records showed the time blood was obtained for the theophylline assay, 26 percent of the records reviewed had no time recorded indicating the patient's last dose of the theophylline drug. Accurate interpretation of the assay result would be impossible without this information, causing wasted time and expense in performing the assay. In addition, the data may be used to make inappropriate changes in

dosage or cause a delay in changes which may be needed by the patient.

In examining the action taken by physicians in response to theophylline serum concentrations judged to be sub-therapeutic (less than 10 mcg/ml) or toxic (greater than 20 mcg/ml), 52.5 percent of patients in these categories had no changes made in theophylline dosage. Excluding from this number the patients who were assessed as doing well at a concentration in the 5 to 9.9 mcg/ml range, this leaves a high percentage (42.6 percent) who had no adjustments in dosage. When changes in dosage were made, 39 percent were judged to be inappropriate changes in response to reported assay values. Since 12 of these inappropriate changes (out of a total of 16) were increased or decreased doses within the 10 to 20 mcg/ml range, it is conceivable that the patient's clinical state may have justified a change. However, no evidence for this was found in reviewing the progress notes. The study by Anderson, Hodges, and Barnes (1976) reported that 48.1 percent of the gentamicin assays examined had not been acted upon appropriately, and in the study on digoxin and digitoxin assays by Slaughter, Schneider, and Visconti (1978) 36 percent of the assays were acted upon inappropriately or had no action taken when the assay result suggested a change in therapy be made. The cause of this high rate of inappropriate action or failure

to act may, in part, be attributable to the problem of inadequate documentation. Incomplete or absent documentation also played a significant role in the finding that only 28 percent of the 100 assays and records reviewed could be assessed as fulfilling all of the study criteria. Improvement in documentation practices would improve this percentage and this suggests that better documentation alone may benefit the patient by making these laboratory tests more useful in appropriately dosing theophylline drugs.

The preceding criteria were also used to test the hypothesis that physicians practicing in the Pulmonary Clinic site use theophylline serum concentration data more appropriately than those in the General Medicine clinics. Since these physicians would be expected to treat more patients who require bronchodilator treatment and as a result order more theophylline assays, it may be reasonable to assume greater knowledge of their proper use. In none of the criteria tested, using chi-square analysis, were any significant differences found between these two groups of physicians in their use of theophylline assays. Since some of the physicians providing data for the study were not pulmonary "specialists", but were doing elective rotations through the Veterans' Administration Medical Center Pulmonary clinics, these results are no more than suggestive of a true absence of differences.

Finally, in examining the outcome of changes in dosage classified as appropriate and inappropriate, a statistically significant difference was found when these changes were related to the physician's assessment of the patient's clinical state. Appropriate dosage changes were found to be far more likely to produce improvement in the patient than dosage changes classified as inappropriate. This was reflected in the finding that 16 of 25 patients (64%) having appropriate dosage adjustments were assessed as improved clinically at their next appointment. Further, 12 of 16 patients (75%) having adjustments in theophylline dosage judged to be inappropriate were assessed as either showing no improvement or deteriorating. Since the physicians' assessments of the patients were in some cases partially subjective, resulting from answers to questions such as "How do you feel?", the differences in response to dosage adjustments are not certain to be cause-and-effect. They are, however, strongly suggestive that clinical improvement results when theophylline serum concentration data are properly used.

This conclusion is supported by the published results of earlier studies. Bootman et al. (1979) determined that the use of pharmacokinetic data to individualize gentamicin therapy resulted in significant improvement in patient recovery and decreased toxicity. Floyd and Cohen (1977)

and Koup et al. (1976) have shown that the use of theophylline serum concentration data to guide therapy can reduce the incidence of toxicity while providing effective doses of these drugs. Scherr, Scherr, and Norton (1980) reported that the use of serum concentrations to achieve optimum dosing of oral theophylline was instrumental in improving the therapy of pediatric asthmatics. The findings of the study reported herein provide further evidence in support of the judicious application of serum concentration data, particularly when the potential exists for serious toxic reactions.

Phase II

In the second part of this study, data were collected and analyzed to test the hypothesis that theophylline serum concentrations are different in patients who have these assays requested by their physician than in those who do not have this laboratory test ordered.

To test this hypothesis, results were obtained from 77 physician-ordered theophylline plasma concentration assays in ambulatory patients. These values were compared to the values obtained in 102 outpatients who had theophylline serum concentrations determined by the investigator after the physician who examined the patient made a decision not to request the assay.

The ages of patients whose assays were physician-ordered ranged from 29 to 85 years, with a mean ($\pm$ S.D.) age of 61.0 ± 9.4 years. One of the 77 patients was a female (1.3%). Ages of the investigator's subjects ranged from 33 to 83 years, with a mean ($\pm$ S.D.) age of 61.3 ± 7.4 years. Two of the 102 subjects were females (1.9%).

The results of the assays ordered by physicians appear in Appendix C, Table C-1. The results from the investigator's subjects are shown in Appendix C, Table C-2. Table 11 shows the number of patients from each group who had theophylline serum concentrations within the ranges indicated as less than 5 mcg/ml, 5 to 9.9 mcg/ml, 10 to 20 mcg/ml and greater than 20 mcg/ml. Chi-square analysis revealed no significant differences between the two groups in numbers of patients having serum concentrations in these ranges ($\chi^2 = 4.157$; $df = 3$; n.s.). Further statistical analysis using Student's t to test for differences between the means of the theophylline serum concentrations found in the physicians' and investigator's patients also showed no significant differences ($t = 1.05$; $df = 177$; n.s.). The mean ($\pm$ S.D) theophylline serum concentration in the physicians' group was 10.96 ± 5.9 mcg/ml, and the mean ($\pm$ S.D.) in the investigator's group was 10.0 ± 6.0 mcg/ml.

As a corollary to this investigation, the physicians' progress notes were reviewed and data tabulated which

Table 11. Number of Theophylline Serum Concentrations within Ranges, from Physicians' and Investigator's Groups

Subject Group	Range of Serum Concentration (mcg/ml)				Total
	<5	5-9.9	10-20	>20	
Physicians' Patients	10 (12.0%)	25 (32.5%)	35 (45.4%)	7 (9.1%)	77 (100.0%)
Investigator's Patients	23 (22.5%)	36 (35.3%)	38 (37.2%)	5 (4.9%)	102 (100.0%)
Total	33 (18.4%)	61 (34.1%)	73 (40.8%)	12 (6.7%)	179 (100.0%)

$\chi^2 = 4.157$; df = 3; n.s.

revealed any complaint of increased difficulty in breathing or a report by patients of any symptom which could be the result of toxic serum concentrations of theophylline. This portion of the investigation was of an exploratory nature, and the analysis of this data was an attempt to show any relationship which existed in the study subjects between nontherapeutic theophylline serum concentrations in these patients and complaints of breathing difficulties or symptoms of theophylline toxicity reported by the physician in his assessment of the patient.

When physicians' assessments were examined to determine if a report of increasing difficulty in breathing could be associated with theophylline serum concentrations which were different from those found in subjects without shortness of breath, a strong trend in the direction of subtherapeutic theophylline concentrations in subjects complaining of increasing dyspnea was found (Table 12). The differences were shown to be statistically significant by chi-square analysis ($\chi^2 = 12.241$; $df = 2$; $p < 0.01$).

Reports by patients of symptoms which have been related to theophylline toxicity were also recorded. These were headaches, irregular heart rhythms, nausea or emesis, dizziness, hypotension, precordial pain, agitation or restlessness, and evidence of seizures were tabulated and

Table 12. Number of Subjects Assessed by Physicians as Having Increased Dyspnea with Sub-Therapeutic, Therapeutic and Toxic Theophylline Serum Concentrations

Physician's Assessment	Serum Concentration (mcg/ml)			Total
	<10	10-20	>20	
Increased Dyspnea	60 (64.5%)	30 (32.3%)	3 (3.2%)	93 (100.0%)
No Change or Improved	34 (39.5%)	43 (50.0%)	9 (10.5%)	86 (100.0%)
Total	94 (52.5%)	73 (40.8%)	12 (6.7%)	179 (100.0%)

$$\chi^2 = 12.241; df = 2; p < 0.01$$

analyzed. Table 13 shows the comparison of theophylline serum concentrations in subjects reporting none of the above symptoms with those in subjects who did complain of one or more symptoms possibly due to theophylline toxicity. The results reveal a definite trend toward increasing symptoms of toxicity as serum concentrations increase. This is borne out by chi-square analysis, which showed a statistically significant difference between the groups ($\chi^2 = 28.264$; $df = 2$; $p < 0.001$).

The findings of no significant difference between the physicians' and investigator's groups in terms of theophylline serum concentrations (Table 11) suggests two possible conclusions. The physicians whose assay orders were used for comparison may have been unable to assess these ambulatory patients as being at risk from sub-therapeutic or toxic theophylline dosages. If this is the case, the clinical signs or patient symptoms which prompted the decision to request an assay would seem to be unreliable indicators of low or high serum concentrations. Support is given this conclusion by the findings of Zwillich et al. (1975) that serious toxic reactions are not always preceded by signs of less severe reactions. In addition, evidence that symptoms may not reliably predict low theophylline serum concentrations has been reported by Eaton et al. (1980). They concluded from their work that patients were not able to distinguish between low and high serum

Table 13. Number of Subjects Assessed by Physicians as Having Symptoms of Possible Theophylline Toxicity with Sub-Therapeutic, Therapeutic and Toxic Theophylline Serum Concentrations

Physician's Assessment	Serum Concentration (mcg/ml)			Total
	<10	10-20	>20	
Symptoms of Toxicity	10 (27.8%)	17 (47.2%)	9 (25.0%)	36 (100.0%)
No Symptoms of Toxicity	84 (58.7%)	56 (39.2%)	3 (2.1%)	143 (100.0%)
Total	94 (52.5%)	73 (40.8%)	12 (6.7%)	179 (100.0%)

$\chi^2 = 28.264; df = 2; p < 0.001$

concentrations of theophylline, or to distinguish between placebo and active drug treatment when measured by subjective improvement in breathlessness at rest. This occurred even though spirometry revealed significant improvement in pulmonary function among patients dosed with theophylline to achieve higher (17-22 mcg/ml) serum concentrations.

It is also possible to conclude that the physicians had ordered assays to determine whether or not patients were receiving the proper dose of theophylline, and not in response to subjective or clinical signs. A total of 106 subjects (59.2%) from both groups had theophylline serum concentrations outside of the therapeutic range, suggesting that close monitoring of these patients is warranted. Once the decision is made to begin theophylline treatment for an ambulatory chronic obstructive pulmonary disease patient, the evidence suggests that appropriate use of assays to determine the dosage necessary to achieve and maintain therapeutic theophylline serum concentrations is the most rational approach.

A complaint of increased difficulty in breathing among subjects in this study was found to be associated with lower theophylline serum concentrations (Table 12). This was an interesting finding because results from the first phase of this study are in sharp contrast to these results. Furthermore, subjects complaining of symptoms related to the theophylline toxicity (Ingram, 1980) were associated

with higher theophylline serum concentrations outside of the therapeutic range. This apparent discrepancy may be the result of changes in physician staffing between Phase I and Phase II in the Pulmonary and General Medicine Outpatient Clinics. It is also possible, though unlikely, that subjects selected for inclusion in the study were more likely to experience the symptoms in question. A more likely explanation is that the subjects were interviewed in more detail about such symptoms and therefore had an opportunity to document these changes. In addition to the emphasis this study has placed upon the proper utilization of theophylline serum concentration data, careful questioning of the patient and documentation seems to be essential to this process and an integral part of safe and effective treatment with these drugs.

CHAPTER 5

SUMMARY AND RECOMMENDATIONS

This study was conducted in two phases, each having two questions which the investigation attempted to answer. In Phase I the medical records of 100 ambulatory chronic obstructive pulmonary disease patients were reviewed to determine if theophylline serum concentration determinations had been ordered and used appropriately in the patients studied. Second, pulmonary physicians were compared with general medicine physicians in terms of their ability to use theophylline assays properly. Phase II examined the question of whether physicians at the study hospital could determine that patients were at risk from sub-therapeutic or toxic serum concentrations of theophylline, as shown by the decision to order the assay. Patient complaints were also examined to determine if, in these subjects, certain complaints were associated with theophylline serum concentrations outside of the therapeutic range.

Analysis of the results from Phase I revealed significant problems in the way theophylline assays were ordered at the study hospital and in documentation and interpretation of the assays. A reason for ordering the assay and the fact that an assay had been ordered were not

indicated in 65 percent of the records reviewed. Considering also that 64 percent of the records revealed no evidence that the assay results were acknowledged or used to change therapy, it is reasonable to suspect that documentation of these laboratory tests and their results is often not shown in the physicians' progress notes. The findings also suggest that assay results are either ignored or simply forgotten in many cases. Additional evidence of this is found in the high percentage (42.6 percent) of patients outside of the 10 to 20 mcg/ml therapeutic range who had no changes in theophylline dosage in response to the assay. These problems could all conceivably be the direct result of poor documentation practices. Since changes in the dosage of oral theophylline in ambulatory patients is frequently done on the basis of clinical signs and symptoms, the judgment that 39 percent of the changes in dosage were inappropriate could have been tempered by simple documentation of the reason for the change. The lack of this documentation played a major role in some of the problems found. Twenty-six of the 100 laboratory orders examined lacked an indication of the time the patient took his last dose of the oral theophylline prior to having the blood sample taken. Since this information is essential to accurate interpretation of the assay result, these assays are of little value unless the results are definitely in the toxic range.

This is even further reason to conclude that a great deal of improvement in the use of these assays could result from an increased emphasis on making written comments in the progress notes when assays are requested, filling out the laboratory order completely, and interpreting the assay result as soon as available.

An interesting finding resulted when the physician's assessment of the patient, at the next examination after a change in dosage was made, was compared to the classification of the change as "appropriate" or "inappropriate". A statistically significant difference was found indicating that a change in dosage classified as "appropriate" was more likely to result in a physician's assessment of the patient's clinical state as improved when compared to dosage changes classified as "inappropriate". A reasonable conclusion is that properly ordered, documented and interpreted theophylline assays which provide accurate, usable results can have the direct result of improving the patient's clinical state.

When Pulmonary Clinic and General Medicine Clinic physicians were compared in terms of their ability to use theophylline assays properly, in none of the seven criteria tested were any significant differences found. The only conclusion supportable by this finding is that the increased

frequency of use of these assays and of theophylline-related drugs had no effect on improving the use of the assays by physicians practicing in the Pulmonary Clinic site.

Statistical analysis of the findings in Phase II produced no evidence that physicians at the study hospital could determine whether ambulatory patients under treatment were at risk from theophylline serum concentrations above or below the therapeutic range of 10 to 20 mcg/ml.

In a preliminary, exploratory investigation a relationship between patient complaints of increasing difficulty of breathing or symptoms of toxicity and serum theophylline concentrations was suggested. Theophylline serum concentrations outside the therapeutic range were related to signs and symptoms of inefficacy and toxicity. This relationship suggests that a more extensive investigation involving patient specific factors possibly related to the serum theophylline concentration may be useful in any attempt to more effectively utilize the assay in patient management.

Oral theophylline related drugs are the mainstay of treatment for many patients with chronic obstructive pulmonary diseases, as well as those with asthma. Since these drugs have been demonstrated to be most effective within a relatively narrow serum concentration and are also associated

with serious toxicity when serum concentrations are excessive, it is reasonable to conclude that patients taking these drugs need to be closely monitored to achieve both safe and effective treatment. Evidence presented here suggests that the physician's examination and clinical assessment of the patient may not reveal ineffective or excessive theophylline dosage. The judicious use of theophylline serum concentration data to achieve and maintain therapeutic doses could result in improvement in patients with a disabling disease while helping to avoid the serious consequences of a possible overdose.

The following recommendations are made in response to the findings of this study:

1. Instructions should be developed with recommendations from the Laboratory, Pharmacy and Medical Services at the Veterans Administration Hospital to advise those ordering or interpreting theophylline assays on their appropriate use. A sheet containing these instructions should be provided to each new physician. An abbreviated form might also be developed to include with the laboratory slip used in reporting results of the assay.

2. The Pharmacy and Therapeutics Committee establish a protocol for the ordering of drug serum concentration determinations.
3. The Pharmacy Service become involved with the Laboratory and Medical Services, in conjunction with the staff Clinical Pharmacist, to improve theophylline therapy by periodic review of medical records and written reports to the Chief of Staff.
4. Efforts be made to place ambulatory patients under the direct care of a single physician whenever possible, rather than having the patient changed to different physicians from one appointment to the next.
5. A stronger emphasis be placed on documentation of laboratory test orders and their results in the physician's progress notes.
6. Consideration be given to the hiring of an additional Clinical Pharmacist so that more time might be available for consistent review and interpretation of drug serum concentration data.
7. This study be expanded to examine more thoroughly the outcome of properly used theophylline serum concentration data in terms of clinical improvement of patients.

8. A study be designed and implemented which examines the relationship between the use of theophylline serum concentration data and the frequency of hospitalizations and emergency room visits. The number of such hospitalizations for subjects who were dosed on the basis of these data should be compared with those who did not have these assays used in their outpatient treatment.
9. A cost-benefit study be done which determines whether or not the proper use of theophylline serum concentration assays can be useful in reducing costs relating to medical care of patients not optimally dosed with these drugs.
10. An investigation be undertaken which attempts to elucidate possible relationships between sub-therapeutic or toxic theophylline serum concentrations and patient risk factors such as other drugs used, other diseases present, smoking history, diet, body weight, or chronic ingestion of ethanol.

APPENDIX A

CONSENT FORM

THEOPHYLLINE SERUM CONCENTRATIONS IN AMBULATORY
PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

I understand that I am being asked to participate in a study to be conducted at the Tucson Veterans' Administration Medical Center. The study is being done to determine how much theophylline (from a drug I am taking to help my breathing) is in my blood and to see how this information is used by my doctors to treat my illness.

If I decide to participate, I understand that I will be asked to answer questions about my past and present health and smoking habits. I will also be asked to allow blood to be taken from my arm by a needle stick, and that the amount of blood I will lose will be 15 ml (about one tablespoonful) or less. I understand that the length of time I will spend participating in this study will be approximately 15 minutes on one afternoon after I have seen my doctor at the V.A. Hospital. I also understand that the risks to me from being in this study are slight, but that I might get a bruise on my arm from the needle stick. Medical assistance will be immediately available to me by Dr. Campbell or one of his associates in the Pulmonary Clinic, should I need it for any reason.

I understand that financial compensation will not be provided to me in exchange for my agreement to participate, nor is such compensation available to me for wages or time lost due to injury incurred in this study. I understand that I will not be charged for any of the laboratory tests done in this study, and that any necessary medical treatment or hospitalization will be provided free of charge in the event I am injured in any way. No immediate benefits will be provided to me from participation in this study, except that of determining how much theophylline is in my blood. The results of this study may be of benefit to me or others in the future by helping to show how to use laboratory tests for drugs in blood more efficiently.

Only the investigators in this study will have access to the information obtained in it, and my name will not be disclosed in any reports. I give permission to the investigators to use the information from this study as they see fit. I also understand that this consent form will be filed in an area designated by the Human Subjects Committee with access restricted to the investigators.

I have read the above Subject's Consent and I understand what my participation in this study involves. I understand that I may refuse to participate or withdraw from the study at any time without incurring ill will, and that more information will be provided by the investigators upon request. I also understand that a copy of this consent form is available to me on my request.

Signature of Subject

Date

APPENDIX B

SURVEY OF ACTIVE DIAGNOSES IN STUDY SUBJECTS
AND TABLE OF METHYLXANTHINE DRUGS
PRESCRIBED AND FREQUENCY

Table B-1. Active Diagnoses in Study Patients and Frequency of Occurrence

Diagnosis	Number of Patients		
	Pulmonary	General Medicine	Total
Chronic Obstructive Pulmonary Disease	50	50	100
Hypertension	10	13	23
Congestive Heart Failure	8	10	18
Alcohol Abuse	9	5	14
Obesity	7	6	13
Arteriosclerotic Heart Disease	5	8	13
Depression	2	5	7
Cor Pulmonale	5	2	7
Asthma	3	4	7
Diabetes Mellitus	2	4	6
Tuberculosis (inactive)	2	3	5
Arthritis			
Rheumatoid	1	2	3
Osteoarthritis	0	2	2
Degenerative Joint Disease	1	1	2
Ankylosing spondylitis	0	1	1
Peptic ulcer disease	2	1	3
Renal insufficiency	1	2	3
Renal failure	0	3	3
Carotid Stenosis	1	1	2
Gout	0	2	2

Table B-1.--Continued

Diagnosis	Number of Patients		
	Pulmonary	General Medicine	Total
Cardiac arrhythmias			
supraventricular			
tachycardia	1	1	2
atrial flutter	0	2	2
Hypothyroid	1	1	2
Seizure history	1	1	2
Schizophrenia	1	1	2
Manic-depressive	0	2	2
Angina	1	1	2
Cancer			
bronchogenic	2	0	2
bladder	1	0	1
chronic lymphocytic	0	1	1
leukemia	0	1	1
basal cell	0	1	1
Hepatic cirrhosis	1	1	2

The following diagnoses were found one time only on any subject's active problem list: diverticulosis, cerebral vascular disease, polycythemia, hypokalemia, urinary tract infection, pneumothorax, goiter, psoriasis, nephrolithiasis, heroin addiction, anemia, herpetic ophthalmic keratitis, malnutrition, cerebral vascular disease, encephalitis, proteinuria, varicose veins, pulmonary fibrosis, hyperlipoproteinuria.

Table B-2. Methylxanthine Products Prescribed in Study
Patients and Frequency

Drug	Number of Patients for Whom Prescribed
Aminophylline	69
Oxtriphylline	21
Theophylline (sustained release)	10

APPENDIX C

RESULTS OF THEOPHYLLINE SERUM CONCENTRATION ASSAYS IN THE PHYSICIAN-ORDERED AND INVESTIGATOR-ORDERED GROUPS

Table C-1. Results of Theophylline Serum Concentration Assays in Physician Ordered Group

Patient Number	Assay Result (in mcg/ml)	Patient Number	Assay Result (in mcg/ml)
1	3.4	25	7.8
2	<2.5		
3	16.2	26	27.0
4	9.2	27	12.1
5	<2.5	28	11.3
		29	< 2.5
6	<2.5	30	3.4
7	9.4		
8	23.4	31	10.6
9	9.1	32	18.4
10	7.2	33	13.3
		34	5.3
11	<2.5	35	7.1
12	8.8		
13	8.0	36	13.7
14	12.7	37	4.0
15	7.5	38	7.0
		39	10.0
16	12.0	40	20.0
17	20.1		
18	11.2	41	13.1
19	14.9	42	10.0
20	23.8	43	6.7
		44	10.9
21	9.8	45	10.8
22	14.8		
23	16.8	46	11.3
24	7.8	*47	6.4

Table C-1.-- Continued

Patient Number	Assay Result (in mcg/ml)	Patient Number	Assay Result (in mcg/ml)
48	10.1	71	7.5
49	3.2	72	13.7
50	20.2	73	14.8
		74	8.1
51	11.3	75	17.2
52	9.3		
53	8.2	76	12.7
54	21.4	77	15.6
55	14.1		
56	11.4		
57	7.0		
58	8.6		
59	5.2		
60	18.9		
61	8.6		
62	8.0		
63	5.9		
64	20.8		
65	10.9		
66	16.1		
67	29.2		
68	10.6		
69	15.3		
70	4.4		

Table C-2. Results of Theophylline Serum Concentration Assays in Investigator's Group

Patient Number	Assay Result (in mcg/ml)	Patient Number	Assay Result (in mcg/ml)
1	5.4	26	12.1
2	<2.5	27	7.7
3	<2.5	28	3.5
4	4.7	29	9.4
5	16.9	30	<2.5
6	3.0	31	21.0
7	<2.5	32	7.7
8	9.6	33	7.0
9	7.0	34	24.3
10	4.6	35	10.8
11	16.1	36	18.7
12	<2.5	37	10.6
13	13.5	38	9.8
14	12.0	39	27.1
15	13.8	40	8.0
16	7.2	41	18.3
17	10.2	42	< 2.5
18	12.7	43	9.0
19	21.2	44	12.6
20	11.6	45	8.2
21	< 2.5	46	19.6
22	16.1	47	
23	6.9	48	7.2
24	14.7	49	9.1
25	3.7	50	6.6

Table C-2.---Continued

Patient Number	Assay Result (in mcg/ml)	Patient Number	Assay Result (in mcg/ml)
51	10.4	76	5.0
52	14.8	77	12.8
53	12.0	78	5.5
54	14.3	79	14.1
55	4.0	80	<2.5
56	18.2	81	13.7
57	13.7	82	< 2.5
58	7.0	83	9.0
59	< 2.5	84	9.3
60	16.6	85	5.7
61	4.4	86	28.4
62	7.7	87	9.9
63	9.9	88	7.5
64	3.2	89	8.3
65	8.0	90	16.7
66	8.0	91	14.4
67	14.6	92	19.8
68	<2.5	93	7.1
69	6.1	94	14.7
70	9.9	95	6.0
71	16.4	96	2.9
72	10.9	97	4.3
73	8.2	98	14.0
74	3.8	99	15.1
75	12.6	100	18.2

Table C-2.--Continued

Patient Number	Assay Result (in mcg/ml)
101	7.7
102	20.0

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